multi-step combinational biopolymer synthesis, including, but not limited to, the synthesis of different oligonucleotides or peptides at specific micro-locations.

Page 10, replace paragraph beginning on line 29 as follows:

The devices are fabricated using both microlithographic and micro-machining techniques. The devices have a matrix of addressable microscopic locations on their surface; each individual micro-location is able to electronically control and direct the transport and attachment of specific binding entities (e.g., nucleic acids, antibodies) to itself. All micro-locations can be addressed with their specific binding entities. Using these devices, the system can be self-assembled with minimal outside intervention.

Page 12, replace paragraph beginning on line 17 as follows:

Thus, the disclosed devices can carry out multi-step and multiplex reactions with complete and precise electronic control, preferably with overall micro-processor control (i.e. run by a computer). The rate, specificity, and sensitivity of multi-step and multiplex reactions are greatly improved at specific micro-locations on the disclosed device.

Page 19, replace paragraph beginning on line 14 as follows:

FIGURE 3 is a schematic representation of a self-addressable 64 micro-location chip.

Page 19, replace paragraph beginning on line 25 as follows:

Fig. 7a and Fig. 7b show the mechanism the device uses to electronically concentrate analyte or reactant molecules at a specific micro-location, Fig. 7a showing the addressable microlocations in a neutral condition and Fig. 7b showing the addressable microlocations in a charged state.

Page 19, replace paragraph beginning on line 28 as follows:

Figs. 8a, 8b, 8c and 8d show the self-directed assembly of a device with three specific oligonucleotide binding entities (SSO-A, SSO-B, and SSO-C), Fig. 8a showing a first microlocation (ML-1) being addressed, Fig. 8b showing a second microlocation (ML-2) being addressed, Figure 8c showing a third microlocation (ML-3) being addressed and Figure 8d showing the three microlocations after being addressed and assembled.

Page 19, replace paragraph beginning on line 31 follows:

Figs. 9a, 9b and 9c show an electronically controlled hybridization process with sample/target DNA being concentrated at micro-locations containing specific DNA capture sequences, Fig. 9a showing specific capture sequences on addressable microlocations, Fig. 9b showing specific and nonspecific DNA adjacent the structure of Fig. 9a, and Fig. 9c showing hybridized material adjacent microlocations ML-1 and ML-3.

Page 20, replace paragraph beginning on line 3 as follows:

Figs. 10a and 10b show an electronically directed serial hybridization process, Fig. 10a showing materials adjacent microlocation ML-3 and Fig. 10b showing materials adjacent microlocations ML-3 and ML-5.

Page 20, replace paragraph beginning on line 5 as follows:

Figs. 11a, 11b and 11c show the electronic stringency control (ESC) of a hybridization process for determining single point mutations, Fig. 11a showing uncharged addressable microlocations, Fig. 11b showing negatively charged microlocations and Fig. 11c showing negatively charged microlocations with material denatured from microlocation ML-3.

Page 20, replace paragraph beginning on line 8 as follows:

Figs. 12a, 12b, 12c and 12d show a scheme for the detection of hybridized DNA without using labeled DNA probe, i.e., electronically controlled fluorescent dye detection process, Fig. 12a showing uncharged microlocations, Fig. 12b showing negatively charged microlocations, Fig. 12c showing uncharged microlocations with dye and Fig. 12d showing positively charged microlocations.

D4

Page 20, replace paragraph beginning on line 12 as follows:

Figs. 13a, 13b and 13c show a scheme of electronically controlled replication of devices, Fig. 13a showing negatively charged addressable microlocations, Fig. 13b showing two opposed substrates, one substrate being that of Fig. 13a and the other being a sister device containing an attachment layer, and Fig. 13c showing two substrates, each of which has sequences bound to the microlocations.

Page 20, replace paragraph beginning on line 14 as follows:

Figs. 14a, 14b, 14c, 14d, 14e, and 14f show a scheme of electronically directed combinatorial synthesis of oligonucleotides, Fig. 14a showing addressable microlocations with blocking groups,

Fig. 14b showing addressable microlocations with blocking groups in combination with a deblocking group, Fig. 14c showing blocked and deblocked addressable microlocations in the presence of monomer C, Fig. 14d showing addressable microlocations in combination with a deblocking group, Fig. 14e showing deblocked cites on microlocation ML-2 in the presence of monomer A and Fig. 14f showing microlocations with blocking groups on the terminal ends of sequences.

Pages 38, replace paragraph beginning on line 14 through page 39, line 24 as follows:

A device can be serially addressed with specific binding entities by maintaining the selected micro-location in a DC mode and at the opposite charge (potential) to that of a specific binding entity. If a binding entity has a net negative charge, then the micro-location to which the binding entity is to be transported would be biased positive. Conversely, a negatively charged micro-location would be used to transport a positively charged binding entity. Options for biasing the remaining micro-locations in the serial addressing process include: biasing all other micro-locations at the opposite charge (counter to the micro-locations being addressed); biasing a limited group of micro-locations at the opposite charge; or biasing just one micro-location (or other electrode) at the opposite charge. In some cases, it will be desireable to strongly bias one or more micro-locations at the opposite charge, while other groups of micro-locations are biased only weakly. This process allows previously addressed micro-locations to be protected during the addressing of the remaining micro-locations. In cases where the binding entity is not in excess of the attachment sites on the micro-location, it may be necessary to activate only one other micro-electrode to affect the free field electrophoretic transport to the specific micro-location. Specific binding entities can be rapidly transported through the bulk solution, and concentrated directly at the specific micro-location(s)

where they immediately becomes covalently bonded to the special surface of the attachment layer. Transportation rates are dependent on the size and charge of the binding entities, and the voltage and current levels used between the micro-locations. In general, transportation rates can range from several seconds to several minutes. The ability to electronically concentrate binding entities, reactants or analytes (70) on a specific micro-location (72) is shown in Figs. 7a and 7b. All other micro-locations can be protected and remain unaffected during the specific binding entity addressing process. Any unreacted binding entity is removed by reversing the polarity of that specific micro-location, and electrophoresing it to a disposal location. The cycle is repeated until all desired micro-locations are addressed with their specific binding entities. Figs. 8a through 8d shows the serial process for addressing specific micro-locations (81, 83, 85) with specific oligonucleotide binding entities (82, 84, 86).

Page 42, replace paragraph beginning on line 1 as follows:

The device and methods allow nucleic acid hybridization to be carried out in a variety of conventional and new formats. The ability of the device to electronically control reaction parameters greatly improves nucleic acid hybridization analysis, particularly the ability of the device to provide electronic stringency control (ESC) to each individual micro-location on an array. In essence, this allows each individual hybridization reaction on a common array to be carried out as a single test tube assay.

Page 42, replace paragraph beginning on line 16 as follows:

Conventional hybridization formats, such as "dot blot" hybridization and "sandwich" hybridization, can be carried out with the disclosed device as well as large scale array or matrix formats.

Page 43, replace paragraph beginning on line 11 as follows:

The electronic addressing of the device with specific oligonucleotides is shown in Figs. 8a through 8d. The addressing of the first specific micro-location (ML-1) (81) with its specific sequence oligonucleotide (SSO-1) (82) is accomplished by maintaining the specific microelectrode (ML-1) at a positive DC potential, while all other micro-electrodes are maintained at a negative potential (Fig. 8(A)). The aldehyde functionalized specific sequence (SSO-1) in aqueous buffered solution is free field electrophoresed to the ML-1 address, where it concentrates (> 10^6 fold) and immediately becomes covalently bound to the surface of ML-1 (81). All other microelectrodes are maintained negative, and remain protected or shielded from reacting with SSO-1 sequence (82). The ML-1 potential is then reversed to negative (-) to electrophorese any unreacted SSO-1 to a disposal system. The cycle is repeated, SSO-2 (84) ---> ML-2 (83), SSO-3 (86) ---> ML-3 (85), SSO-n ---> ML-n until all the desired micro-locations are addressed with their specific DNA sequences (Fig. 8(D)).

Page 44, replace paragraph beginning on line 26 as follows:

An example of an electronically controlled hybridization process is shown in Figs. 9a through 9c. In this case, each addressable micro-location has a specific capture sequence (90). A sample solution containing target DNA (92) is applied to the device. All the micro-locations are

activated and the sample DNA is concentrated at the micro-locations (Fig. 9(B)). Target DNA molecules from the dilute solution become highly concentrated at the micro-locations, allowing very rapid hybridization to the specific complementary DNA sequences on the surface. Reversal of the micro-electrode potential repels all un-hybridized DNA from the micro-locations, while the target DNA remains hybridized (Fig. 9(C)). In similar fashion, reporter probes are hybridized in subsequent steps to detect hybridized complexes.

Page 45, replace paragraph beginning on line 19 as follows:

Another common format for DNA hybridization assays involves having target DNAs immobilized on a surface, and then hybridizing specific probes to these target DNAs. This format can involve either the same target DNAs at multiple locations, or different target DNAs at specific locations. Figs. 10a and 10b shows an improved version of this serial hybridization format. In this case micro-locations (101-107) are addressed with different capture DNAs. These are hybridized in a serial fashion with different sequence specific oligonucleotides (108,109). The micro-locations are sequentially biased positive to transport molecules to itself and then biased negative to transport molecules to the next micro-location. At the proper electrode potential, the specifically hybridized DNA probes will remain at that micro-location, while un-hybridized probes are transported to the next micro-location. The sequence specific oligonucleotides probes can be labeled with a suitable reporter group such as a fluorophore.

Page 46, replace paragraph beginning on line 4 as follows:

The disclosed device is able to provide electronic stringency control. Stringency control is necessary for hybridization specificity, and is particularly important for resolving one base mis-

matches in point mutations. Figs. 11a through 11c shows how electronic stringency control can be used for one base mis-match analysis. Electronic stringency control can also be applied to multiple-base mis-match analysis. In Figure 11(A)the perfectly matched DNA hybrid (110) is slightly more stable than mis-matched DNA (112) hybrid. By biasing the micro-locations negative (Fig. 11(B)) and delivering a defined amount of electrophoretic power in a given time, it is possible to denature or remove the mis-matched DNA hybrids while retaining the perfectly matched DNA hybrids (Fig. 11 (C)). Figure (15) compares the results for an electronic hybridization process utilizing electronic stringency control with a conventional hybridization process. The hybridization involves 15-mer G and A point mutation probes for the Ras 12 oncogene mutation. The electronic hybridization result show greatly improved hybridization efficiency and a very large discrimination ratio for the one base mis-match over the conventional procedure.

Page 48, replace paragraph beginning on line 29 through page 49, line 16 as follows:

The ability to provide electronic stringency control to hybridizations also provides new mechanisms for detecting DNA hybridization without using a reporter group labeled DNA probe. It provides a way to carry out a more direct detection of the hybridization process itself. A fluorescent dye detection process is shown in Figs. 12a through 12d and described in Examples 4 and 6. Direct detection of DNA hybrids can be achieved by using DNA binding dyes such as ethidium bromide. The dye binds to both double-stranded and single-stranded DNA but with a greater affinity for the former. In Figure 12(B) positively charged dye (122) is transported to negatively biased micro-locations. The dye binds to both hybridized (120) and unhybridized (121) DNA sequences (Fig. 12C). By biasing the micro-locations positive and delivering a defined amount of power in a given amount of time, the dye molecules bound to un-hybridized micro-locations is selectively removed.

A proper amount of potential can be applied which does not adversely affect the DNA hybrids. The hybridized DNAs with associated dye molecules are then fluorescently detected using associated or integrated optical systems.

D12

Page 51, replace paragraph beginning on line 2 as follows:

D13

In addition to separately addressing individual devices with specific binding entities, it is also possible to produce a master device, which can copy specific binding entities to other devices. This represents another method for the production or manufacture of devices. The process for the replication of devices is shown in Figs. 13a through 13c. A master device containing micro-locations which have been addressed with specific binding sequences is hybridized with respective complementary DNA sequences (130). These complementary sequences are activated and thus capable of covalent binding to the micro-location attachment layer.

Page 54, replace paragraph beginning on line 11as follows:

D14

One method for combinatorial oligonucleotide synthesis is shown in Figs. 14a through 14f. This method begins with a set of selectively addressable micro-locations (140) whose surfaces have been derivatized with blocked primary amine (X-NH-) groups (142). The initial step in the process involves selective deblocking of micro-locations using a charged deblocking reagent (144). In this case, the reagent would carry a positive (+) charge. The process is carried out by applying a negative potential to those micro-locations being de-blocked, and a positive potential to those which are to remain protected (Fig. 14(B)). Application of positive and negative potentials to selective electrodes causes the charged reagents to be moved from a reagent

delivery site and concentrated at the desired micro-location being de-blocked, while excluding reagents from the other micro-locations.

Page 60, replace paragraph beginning at line 5 as follows:

The following oligomers contain 3'-ribonucleoside termini (U):

ET-12R	5'-GCT AGC CCC TGC TCA TGA GTC TCU (Sequence No. 1)
CP-1	5'-AAA AAA AAA AAA AAA AAA AAU (Sequence No. 2)
AT-A1	5'-CTA CGT GGA CCT GGA GAG GAA GGA GAC TGC CTG U (Sequence No. 3)
AT-A2	5'-GAG TTC AGC AAA TTT GGA GU (Sequence No. 4)
AT-A3	5'-CGT AGA ACT CCT CAT CTC CU (Sequence No. 5)
AT-A4	5'-GTC TCC TTC CTC TCC AGU (Sequence No. 6)
AT-A5	5'-GAT GAG CAG TTC TAC GTG GU (Sequence No. 7)
AT-A6	5'-CTG GAG AAG AAG GAG ACU (Sequence No. 8)
AT-A7	5'-TTC CAC AGA CTT AGA TTT GAC U (Sequence No. 9)
AT-A8	5'-TTC CGC AGA TTT AGA AGA TU (Sequence No. 10)
AT-A9	5'-TGT TTG CCT GTT CTC AGA CU (Sequence No. 11)
AT-A10	5'-CAT CGC TGT GAC AAA ACA TU (Sequence No. 12)

Page 61, replace paragraph beginning at line 1 as follows:

The following oligomers contain 5'-amino termini:

ET-21A	5'-Amino-TGC GAG CTG CAG TCA GAC AT (Sequence No. 13)
ET-10AL	5'-Amino-GAG AGA CTC ATG AGC AGG (Sequence No. 14)
ET-11AL	5'-Amino-CCT GCT CAT GAG TCT CTC (Sequence No. 15)
T-2	5'-Amino-TTT TTT TTT TTT TTT TTT T (Sequence No. 16)
RC-A1	5'-Amino-CAG GCA GTC TCC TTC CTC TCC AGG TCC ACG TAG (Sequence No. 17)
RC-A2	5'-Amino-CTC CAA ATT TGC TGA ACT C (Sequence No. 18)

RC-A3	5'-Amino-GGA GAT GAG GAG TTC TAC G (Sequence No. 19)
RC-A4	5'-Amino-CTG GAG AGG AAG GAG AC (Sequence No. 20)
RC-A5	5'-Amino-CCA CGT AGA ACT GCT CAT C (Sequence No. 21)
RC-A6	5'-Amino-GTC TCC TTC TTC TCC AG (Sequence No. 22)
RC-A7	5'-Amino-GTC AAA TCT AAG TCT GTG GAA (Sequence No. 23)
RC-A8	5'-Amino-ATC TTC TAA ATC TGC GGA A (Sequence No. 24)
RC-A9	5'-Amino-GTC TGA GAA CAG GCA AAC A (Sequence No. 25)
RC-A10	5'-Amino-ATG TTT TGT CAC AGC GAT G (Sequence No. 26)

Page 69, replace paragraph beginning at line 27 through page 70, line 15 as follows:

The APS (3-aminopropyltriethoxysilane) process involves reacting the entire surface of the chip. Selectivity of this initial functionalization process is dependent on the relative reactivities of the various materials on the chip surface. In order to reduce functionalization and subsequent DNA attachment to the areas surrounding the micro-locations, a material that is less reactive to APS than SiO_2 or metal oxide is needed. Photoresists and silicon nitride were tested. The different topcoats were applied to silicon dioxide chips. The chips were examined by epifluorescence and then treated with APS followed by covalent attachment of periodate oxidized poly-A RNA sequences (Sigma, M 100,000). The chips were hybridized with 200 nM solution of Texas Red labeled 20-mer (T2-TR) in hybridization buffer, for 5 minutes at 37°C. The chips were washed 3 times in washing buffer and once in 1 x SSC. The chips were examined by fluorescence at 590 nm excitation and 610 nm emission.

Page 71, replace paragraph beginning at line 9 as follows:

The initial fabrication consisted of the silicon substrate, a silicon dioxide insulating layer, aluminum deposition and patterning, and a silicon nitride topcoat.

Page 71, replaced paragraph beginning at line 19 as follows:

An 8 x 8 matrix chip was functionalized with APS reagent as described in Example 5. The chip was then treated with periodate oxidized poly-A RNA (Sigma, average M 100,000). The chip was washed in washing buffer (WB) to remove excess and unbound RNA. This process coated the entire chip with the capture sequence, however there is a much higher density at the exposed metal surfaces than at the nitride covered areas. The chip was hybridized with a 200 nM solution of T2-TR in hybridization buffer (HB) for 5 minutes at 37°C, and then washed 3 times in WB and once in 1XSSC for one minute each at ambient temperature. The chip was examined by fluorescence at 590 nm excitation and 610 nm emission.

Page 75, replace paragraphs beginning at line 29 through page 76, line 7 as follows:

The attachment sequences were:

Ras-G 5'- GGT GGT GGG C**B**C CG**B** CGG TGT GGG CAA GAU-3'- micro-location (Sequence No. 27)

Ras-T 5'- GGT GGT GGG C**G**C CGT CGG TGT GGG CAA GAU-3'- micro-location (Sequence No. 28)

The reporter probe sequences (labelled with Texas Red) were:

Ras-1 3'-CC-G**C**G-GC**C**-GCC-ACA-C-5'-(TR) (Sequence No. 29)

Ras-2 3'-CC-G**C**G-GC**A**-GCC-ACA-C-5'-(TR) (Sequence No. 30)

Ras-3 3'-CC-G**T**G-GC**A**-GCC-ACA-C-5'-(TR) (Sequence No. 31)

Page 78, replace paragraph beginning at line 12 as follows:

Ras-G 5'-GGT GGT GGG C**G**C CG**G** CG**G** TGT GGG CAA GAU (Sequence No. 32)

Ras-GA 5'-Amino-GGT GGT GGG C**G**C CG**G** CG**G** TGT GGG CAA GA (Sequence No. 33)

Ras-22C-TR (TR)-5'-TGC CCA CAC CG**C** CGG CGC CCA C (Sequence No. 34)

Ras-22A-TR (TR)-5'-TGC CCA CAC CG**A** CGG CGC CCA C (Sequence No. 35)

Ras-TA (TR)-5'-TGC CCA CAC CG**A** CGG **T**GC CCA C (Sequence No. 36)

D21

Ras-7C (TR)-5'-ACA **C**CG C (Sequence No. 37)

Ras-7A (TR)-5'-ACA **A**CG C (Sequence No. 38)

Page 89, replace paragraph beginning at line 1 as follows:

D22

The various M13 attachment and probe sequences used in this example are prepared as previously described in the specifications. These sequences are shown below:

M13-C1 5'-CCA GTC ACG ACG TTG TAA AAC GAC GGC CAG U (Sequence No. 39)

M13-C2 5'-GTA ATC ATG GTC ATA GCT GTT TCC TGT GTG U (Sequence No. 40)

MP18-40C 5'GCA TGC CTG CAG GTC GAC TCT AGA GGA TCC CCG-GGT ATT C (Sequence No. 41)

M8-40C 5'-TGC CAA GCT TGG CTG CAG GTC GAC GGA TCC- CCG GGT ACC G (Sequence No. 42)

M18-R1 (TR)-5'-AAA TTG TTA TCC GCT CAC AAT TGC (Sequence No. 43)

MP8-R2 (F)-5'-ACA CAA CAT ACG AGC CGG AAG CAT (Sequence No. 44)